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Familial Risk of Psychosis as a Function of Putative Organic Etiology in Psychotic Probands: Evaluation of a Population-Based Sample

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It is unresolved what, if any, characteristics should be used as a basis for assigning psychotic probands to different liability classes in high density family studies seeking to detect possible genetic linkage. Justification for any such assignments should ideally ensue from empirical evaluation of unselected samples. It has been suggested that the genetic liability of probands with an "organic" psychosis is lower than that found in "primary" cases. Should such cases be assigned differential liabilities in linkage analyses as one way of modeling etiologic heterogeneity?

Utilizing data from a population-based family study conducted in County Roscommon in Western Ireland, we examined risk in the relatives of psychotic probands as a function of clinician ratings reflecting the probability that the proband's illness was organic. Contrary to expectation, risk was not significantly lower in relatives of probands whose illness was rated as organic by experienced clinicians. Attempts to identify possible phenocopies of psychosis with a lower familial liability in this treated epidemiologic sample were unsuccessful.

KEY WORDS: psychosis, schizophrenia, phenocopy, organic

INTRODUCTION

A range of medical disorders are associated with psychosis at a rate exceeding chance expectations [Davison and Bagley, 1969; Davison, 1983; Cummings, 1988]. These include: epilepsy [Slater et al., 1971; Diehl, 1989], cerebral trauma, cerebral tumor, the encephalitides, various degenerative and cerebrovascular disorders [Davison, 1983], and a range of drug-induced states [Hurlbut, 1991]. The utility of distinguishing these so-called organic psychoses from those of unknown etiology is an important conceptual issue [Rodgers, 1987], both for academic psychiatry and for research aiming to evaluate etiologically and/or genetically informative hypotheses.

The term organic was recently eliminated from DSM-IV [American Psychiatric Association (APA), 1994], which now distinguishes mental disorders due to a general medical condition from those that are substance induced and those that are *primary* mental disorders. Such primary disorders have no demonstrable specific, and direct, causative physiological mechanisms associated with a general medical condition [APA, 1994]. Demonstrating the presence of such mechanisms is, in practice, however, very difficult, and clinical judgment will commonly be employed to assign an individual to an organic, or general medical disorder, group.

Some consider these symptomatic psychotic conditions to reflect phenocopies which lack the genetic loading for "true" schizophrenia [Davison, 1983; Johnstone et al., 1987]. Others, in contrast, have suggested that it is in those with a genetic predisposition that the occurrence of brain pathology is more likely to result in psychosis [Feinstein and Ron, 1990]. Genetically informative data that address differential familial risk of psychosis for organic vs. primary disorders is limited. Davison [1983] summarized most of the data available until the mid 1980s and inferred that, in general, the hereditary loading for psychoses is lower in the relatives of probands with organic cerebral disorder (epilepsy, cerebral trauma, multiple sclerosis, and a heterogeneous patient group), though not in a small series of probands with cerebral tumor [Wanner, 1950 cited in Davison, 1983]. Schulz [1932, abstracted and reviewed in Kendler and Zerbin-Rüdin, submitted] reported a significantly lower risk of schizophrenia in the sibs of schizophrenic probands rated as having a possible or probable physical basis to their illness vs. those

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rated as lacking any such factor. Schulz noted the reduced risk was largely associated with head trauma in probands. Johnstone et al. [1987] reported no definite family history of schizophrenia in cases of first episode schizophrenia for whom organic disease of possible or probable etiological significance was found (syphilis, alcohol excess, sarcoidosis, drug abuse, carcinoma of the lung, autoimmune multisystem disease, epilepsy, thyroid disease, and head injury).

Formanek [1939, cited in Davison, 1983] reported, however, that the presence of extracerebral medical disorders in schizophrenic probands did not predict a lower risk in relatives. Feinstein and Ron [1990] also found no evidence of a lower familial loading of schizophrenia in the relatives of a series of carefully evaluated probands with psychosis and an associated medical condition (epilepsy, head trauma, space-occupying brain lesions, multiple sclerosis, infections, movement disorders, vascular pathology, alcohol abuse, myasthenia gravis, primary hypoparathyroidism, and unexplained encephalopathy).

Despite the considerable effort extended by these previous investigators, all have sampled from specialized treatment centers and/or hospitals where selection bias may operate. To our knowledge there are no reports in the literature examining familial risk as a function of the proband's putative organic status in a treated epidemiologic sample. We therefore aim to compare the risk of illness in relatives of probands rated as organic vs. primary cases by experienced psychiatrists. We emphasize that these judgments are based only on clinician ratings that utilize both hospital records and detailed case summaries provided by field interviewers. Although, therefore, they are not comparable to the detailed evaluations undertaken by some [*cf.* Feinstein and Ron, 1990], such clinical judgments are likely, in practice, to predominate in surveys whose primary purpose is other than documenting the nature of organic states associated with psychosis. Given the weight of the existing evidence we hypothesize a lower risk of psychoses in the relatives of probands with a putative organic basis to their psychosis.

Data analyzed here are a subset of that collected for the Roscommon Family Study (RFS), a treated epidemiologically based study of major mental illness in a rural county in the west of Ireland. As the RFS has previously been described in some detail [see Kendler et al., 1993a,b,c], only a brief outline of the sample shall be given here. Three initial proband groups were ascertained: 1) "schizophrenic" - all cases with a diagnosis of schizophrenia from the Roscommon County Case Register; 2) "affective"—a randomly chosen subsample of 75% of the cases from the Case Register with a diagnosis of major affective disorder; and 3) "control"—age and sex matched controls chosen from the county electoral register. Attempts were made to blindly interview all probands and their first degree relatives aged 16 years and above. All available psychiatric hospital records for probands and relatives were also obtained and abstracted. Both interview data and hospital records, or either when only one source of data was available, were used to formulate Axis 1 diagnoses following DSM-III-R criteria.

The case records of probands with a psychotic illness were examined, and note made of those rated as having an illness of putative organic origin. Two experienced psychiatrists (K.S.K. and Alan M. Gruenberg, MD) had previously rated the likelihood of such a factor based on review of all available hospital records and the interviewer's detailed case summaries, which were based on information elicited by the Structured Clinical Interview for DSM-III-R. The psychiatrist's ratings were made blindly to the proband's family history. Likelihood of organic etiology was rated on a 4-point scale reflecting the confidence of the rater in the assignment (absent vs. possible, probable, or definite). Cases assigned a putative organic etiology were reviewed systematically by the first author, and, after consultation with one of the original raters (K.S.K.), 4 cases were reassigned as lacking such a factor. There were 214 probands diagnosed as having a psychotic illness, specifically 124 with schizophrenia, 40 with schizoaffective disorder, 47 with other nonaffective psychoses and 3 with schizotypal personality disorder/paranoid personality disorder (spd/ppd). Of these 18 (8.4 %) were rated as organic cases. Of those diagnosed as schizophrenic, 7 (5.6%) were rated as organic, of those with schizoaffective disorder 6 (15%) were so rated, of those with another nonaffective psychoses, 5 (10.6%) were rated as organic and of those with spd/ppd none were rated as organic. The rated medical conditions were: epilepsy (N = 3); alcoholism (N = 5); other drug abuse (marijuana, LSD, heroin; N = 2); mental handicap (mild to moderate; N = 3); multiple sclerosis (N = 1); head injury (N = 2); meningitis (N = 1); and influenza (N = 1). Diagnostic data were available on relatives of 196 probands rated as having a primary psychosis. Diagnoses were assigned hierarchically, namely schizophrenia over schizoaffective disorder over another nonaffective psychosis over schizotypal personality disorder. Additional details may be obtained from Kendler et al. [1993a,b,c]. Detailed morbidity risk estimates for a range of disorders have previously been published [Kendler et al., 1993a,b,c] and will not, therefore, be replicated here.

Familial risk in adult relatives of psychotic probands, rated as organic vs. primary cases, was compared using regression analyses of survival data based on the Cox Proportional Hazards model [Cox, 1972]. This model is used to explain the effect of explanatory variables, or covariates, on survival times, in this case age at onset of a psychotic illness, or current age in those without such an illness (such individuals are considered "censored" within these analyses). The covariates included in these models were: the rated basis of the proband's illness (organic vs. primary), the relative's sex, and relationship to the proband (parent, sib, or child), and the source of information used to assign a diagnosis (hospital record without personal interview vs. personal interview and available records). The proportion of proband's relatives who were personally interviewed, vs. those for whom only hospital records were available, was similar for the organic and primary psychotic proband groups (95.8% and 96.9% of relatives, respectively, Fishers Exact Test [2 tailed] χ^2=0.18, df = 1, $P < 0.66$). In these models, putative organicity was entered as a dichotomous variable; 0 = factor rated as ab-

sent; 1 = factor rated as possibly, probably, or definitely present. The same analyses were rerun using the original 4-point rating scale. The results are highly similar to those presented here, and are available on request. All models were run using the statistical package SAS [SAS Institute Inc., 1989].

Table I summarizes the risk ratio (*RR*) of psychoses in relatives as a function of clinician's ratings that the proband's illness was organic or primary, controlling for the covariates outlined above. In Table I, the RR is given for all combinations of narrow (schizophrenia, sz) through broad (schizophrenia or schizoaffective disorder *or other nonaffective* psychosis or schizotypal/paranoid personality disorder, sz spectrum) diagnostic assignments for probands and their relatives—9 alternative combinations in all. In the first entry in Table I, for example, the RR is computed for relatives of probands diagnosed as having schizophrenia (sz) vs. those who received any other diagnosis (schizoaffective disorder, other nonaffective psychosis, schizotypal/paranoid personality disorder). Relatives were considered affected if they also received a diagnosis of schizophrenia. Relatives receiving any other diagnosis, or no diagnosis, were considered unaffected, or censored, in this first analysis. The significance of this differential familial risk is given by the P value associated with the RR estimate.

There is no evidence of a lower risk of psychosis in the relatives of psychotic probands rates as having an organic illness. In fact, risk of schizophrenia is signifi*cantly higher* in the relatives of organic probands (RR = 3.4–3.9). In the analyses summarized in Table I, the diagnostic hierarchy applied progressively added relatives with other psychotic conditions to the "affected" category (which always included relatives with schizophrenia). To determine if there was an increase in risk for any of the other psychotic disorders, independent of that for schizophrenia, a series of additional analyses were conducted to evaluate the RR for each of these disorders considered separately. The RR for schizoaffective disorder, other nonaffective psychosis, or schizotypal personality disorder in relatives did not differ for relatives of organic vs. primary probands, irrespective of the diagnostic hierarchy applied to probands (results available on request). The elevated risk in relatives of probands rated as organic cases applies only to schizophrenia in this population-based sample.

These data contrast with previously published reports, including that by Schulz [1932] and those summarized by Davison [1983] but *cf.* Wanner [1950] and Formanek [1939]. Such findings are, however, in accord with the more recent report by Feinstein and Ron [1990]. They reported a 3.8% risk of schizophrenia in relatives of probands with organic psychoses. This figure was uncorrected for age, and based on the family history method of assessment, and is, therefore, likely to significantly underestimate the true level of morbid risk. No control group was included, however, due to the highly selected nature of the sample. The possibility of differential (i.e., elevated) familial risk was, therefore, not addressed.

In the present study a significantly elevated risk of schizophrenia, but not other psychotic disorders, in the relatives of organic vs. primary probands should be interpreted cautiously. Firstly, like Feinstein and Ron [1990] and Formanek [1939], the present study evaluated familial risk for an organic group with heterogenous features. It may be inappropriate to pool such cases as some organic disorders may themselves be heterogenous etiologically. In large scale population surveys such as that reported here, however, such organic features are still relatively rare and do not allow rigorous evaluation of differential risk by organic subtype.

Such caveats not withstanding, as Feinstein and Ron [1990] note, their findings, and the present data, challenge the notion that genetic and environmental factors relevant to schizophrenia are at opposite poles of an etiological continuum. Such data do not support a purely additive model of genetic and environmental risk factors. If such were the case, probands exposed to a "predisposing" environment, such as that afforded by the presence of the medical conditions rated here, would have, on average, a lower genetic risk for illness than individuals who become ill in a "protective" environment (i.e., in the absence of medical conditions associated with/precipitating psychosis). Feinstein and Ron's [1990] suggestion that certain types of brain pathology are more likely to result in the development of psy-

TABLE 1. Risk of Psychosis in Relatives as a Function of Clinicians Ratings Regarding the Probability the Proband's Illness is Organic*

Diagnosis		No. probands	No. relatives			
Proband	Relative	(organic vs. primary)	(affected vs. censored)	χ^2 (df = 1)	P<	RR
sz	sz	7,117	22,332	5.71	0.02	3.88
	sz sad onap		34,320	2.22	0.13	2.26
	sz spectrum		59,295	1.80	0.18	1.80
sz sad onap	sz	18,193	35,608	9.76	0.002	3.53
	sz sad onap		55,558	3.43	0.06	2.03
	sz spectrum		93,550	2.04	0.15	1.58
sz spectrum	sz	18,196	36,615	9.31	0.002	3.41
	sz sad onap		56;595	3.29	0.07	2.00
	sz spectrum		94,557	2.02	0.15	1.58

*RR = relative risk estimated based on Cox proportional hazards model; sz = DSM-III-R schizophrenia; sad = DSM-III-R schizoaffective disorder; onap = DSM-III-R nonaffective psychosis; sz spectrum = DSM-III-R schizophrenia, schizoaffective disorder, other nonaffectve; psychosis, schizotypal/paranoid personality disorder.

chosis in those with the necessary genetic predisposition, may apply here [see also, e.g., Tsuang et al., 1982; Vardy and Kay, 1983].

Models that consider the joint effect of genes and environment on liability to psychiatric illness [Kendler and Eaves, 1986] may provide an empirical basis for hypothesizing why an elevated risk of schizophrenia was found here in the relatives of cases rated as organic. In a model postulating genetic control of sensitivity to the environment, for example, the risk in relatives can be greater when the proband is exposed to a predisposing environment than if the proband is exposed to a protective environment, if the predisposing environment is relatively common [Kendler and Eaves, 1986]. A model that postulates both genetic control of mean liability to illness (as seen in a simple additive model) and genetic control of sensitivity to the environment may be more applicable here. As the so-called predisposing environment in the present case is, however, heterogeneous (i.e., exposure to drugs or alcohol, infections, or accidental trauma) such a model may only apply to a subset of the cases examined, but may be sufficient to increase the RR for the relatives of this proband group as a whole.

However these risk data are interpreted, it is clear that the identification of phenocopies of schizophrenia, or other psychoses, could not be made by experienced clinicians on the basis of a medical history obtained from hospital records and detailed case notes based on structured psychiatric interview alone. Given the possibly heterogeneous etiology underlying many of the medical conditions associated with schizophrenia, it may be most prudent to include all cases who meet psychiatric criteria in future genetic investigations. If linkage studies yield positive findings, these conditions may then be evaluated for their role in identifying etiological homogeneity or heterogeneity.

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